REMARKS

The Office Action dated December 30, 2004, has been received and reviewed. Claims 1, 4-7, 11, 33-34 stand rejected. Applicants respectfully request reconsideration of the application as amended herein and in view of the arguments below.

I. Claim Amendments

Applicants have added claim 35-37. Support for this amendment for Claim 35 may be found on page 3, line 29 to page 4, line 24. Further support for this claim may be found on page 5, lines 12-14 which recites "The new $\sigma_{1\beta}$ variant finds particular use in the non-invasive diagnosis of cancer and more particularly in the diagnosis of proliferative cancer cells." Claims 36-37 find support in Claim 1.

II. Rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 4-7, 11 and 33 stand rejected as allegedly being indefinite because "it is not clear what activity $\sigma_{1\beta}$ exhibits that is termed a "σ_2 activity". As noted in the specification and throughout the present response, $\sigma_{1\beta}$ exhibits **a substantial increase (about four- fold) in σ_2-like binding**, page 5, lines 8-9. The Application further states "[b]ecause this new variant exhibits σ_2-like binding, it is useful in the screening of compounds useful in the detection of the proliferation state of tumors, as well as in other uses." Page 5, lines 10-12. Additionally, it is noted that "The density of $\sigma_{1\beta}$ in a cell can be determined by measuring the ability of the cell to bind ligands to the $\sigma_{1\beta}$ receptor. The density of the $\sigma_{1\beta}$ receptor may also be determined by measuring the "σ_2-like" binding of the sigma receptors on the cell." Page 6, lines 26-30. The $\sigma_{1\beta}$ receptor exhibits σ_2-like binding, as described in the experimental detail. Applicants note that the specification also recites that "[t]he σ_2-like binding of $\sigma_{1\beta}$ receptors of, for example, tumor cells may be determined and then compared to the same measurement of the tumor cells taken at an earlier time. An increase in the amount of σ_2-like binding over the first or earlier measurement may indicate that the tumor has shifted to a more proliferative status." Page 35, lines 27-31. Furthermore, Example 4 illustrates the determination of the σ_1 specific and σ_2-like binding activity. **Example 4 illustrates a ratio of $\sigma_{1\beta}$ to σ_2 of over 4**. Thus, Applicants submit that a ratio that may be an indicator of the proliferate state of cells has been disclosed. Accordingly, Applicants submit that the phrase "

σ_2 activity" has support in the specification and respectfully request that the rejections to Claims 1, 4-7, 11 and 33 be withdrawn.

III. Rejections under 35 U.S.C. § 101

Claims 4-7, 11 and 33 stand rejected under 35 U.S.C. § 101 as allegedly not being supported by a specific and substantial asserted utility or well established utility. Applicants respectfully disagree with this assertion.

This case clearly states an adequate utility consistent with the guidelines set forth in the *Utility Examination Guidelines,* Federal Register 66, 1092 (January 5, 2001). Applicants note that the specification also states with regard to the $\sigma_{1\beta}$ receptor, "[b]ecause this new variant exhibits σ_2-like binding, **it is useful in the screening of compounds useful in the detection of the proliferation state of tumors**, as well as in other uses. **The new $\sigma_{1\beta}$ variant finds particular use in the non-invasive diagnosis of cancer and more particularly in the diagnosis of proliferative cancer cells**." Page 5, lines 10-14. Applicants further note the specification discloses that the methods of determining the proliferative status of cancer cells are carried out by determining the ability of proliferative cells to bind σ_1 and $\sigma_{1\beta}$ ligands, respectively. The ratio of $\sigma_{1\beta}$ to σ_1 density on a cell is an indicator of the proliferative state of the cell. In one embodiment, the methods are carried out by contacting the cells with a detectably labeled σ_1 receptor ligand and a detectably labeled $\sigma_{1\beta}$ receptor ligand, and determining the extent to which the ligands bind to the cells, wherein the extent provides a measure of the proliferative status of the cell. In other words, the method may be carried out by determining the density of σ_1 receptors and $\sigma_{1\beta}$ receptors of the cell, wherein density is measured by the amount of binding of σ_1 receptor ligands to σ_1 receptors and the amount of binding of $\sigma_{1\beta}$ receptor ligands to $\sigma_{1\beta}$ receptors. The respective densities of $\sigma_{1\beta}$ receptors to the density of σ_1 receptors of the cell, are indicative of the proliferative status of the cell, wherein a higher density of $\sigma_{1\beta}$ receptors as compared to σ_1 receptors indicates that the cancer cells are in a proliferative state. In particular, a ratio of density of $\sigma_{1\beta}$ receptor binding to density of σ_1 binding greater than about 1.5 or 2, or preferably greater than about 3, or even more preferably greater than about 5, and most preferably greater than about eight or ten, indicates that the cell is in a proliferative state. Alternatively, the σ_2-like binding of $\sigma_{1\beta}$ receptors of, for example, tumor cells may be

determined and then compared to the same measurement of the tumor cells taken at an earlier time. An increase in the amount of σ_2-like binding over the first or earlier measurement may indicate that the tumor has shifted to a more proliferative status. Page 35, lines 8-31.

Applicants submit that this application is not a case where no utility is stated; this is not a case where a vague utility (e.g., "biological activity") is stated; this is not a case where an arguable incredible utility (e.g., treating an intractable disease) is stated; this is not a case where a "throw away" utility is stated. To the contrary, in the present application it is noted **that sigma receptors are useful as markers in the non-invasive detection and visualization of a wide variety of tumors using single photon emission computed tomography and positron emission tomography technology.** *See,* Specification, page 2, lines 4-6. Additionally, sigma receptors are abnormally expressed, e.g. overexpressed in tumor cells providing an established use. *See,* page 2, line 31 and page 6, lines 30-32. Particularly, σ_2 receptors were found to be expressed eight to ten times more in proliferative (P) tumor cells than in quiescent (Q) tumor cells. Specification, *p*age 3, lines 33-34. In one study, the σ_2 receptor P:Q ratio was about 10.6 in solid tumors and about 9.5 in a tissue culture study. Wheeler et al., *Br. J. Cancer* 86, 1223-1234 (2000). This would allow one of skill in the art to better diagnose cancer and other disorders of cell proliferation. Specification, *p*age 6, lines 8-13 notes that the compounds of the present application allow for such uses as diagnostic compounds for the imagining of tumor cells. These compounds are also useful as therapeutics for the treatment of cancer and other disorders of cell proliferation. The ligand compounds of the present application are also useful in methods of determining the proliferative status of a tumor. *See,* specification, page 6, lines 8-13. Furthermore, the methods and compositions of the present invention are useful in relation to non-cancer disorders of cell proliferation. These diseases include, but are not limited to, benign tumors, hyperplasias, hyperpigmentation of the skin, psoriasis, and any other disorder wherein cell proliferation is uncontrolled, and control, diagnosis, or imaging of such proliferation is desired. *See,* specification, page 10, lines 17-22.

Applicants also note that the $\sigma_{1\beta}$ receptor exhibits σ_2-like binding, as described in experimental detail below. Applicants submit that the σ_2 receptor activity plays a role in tumor cell proliferation and induction. As such, methods for determining the proliferative state of a cell by determining the cell's ability to bind σ_2 receptors may now be carried out

using a cell's ability to bind $\sigma_{1\beta}$. *See*, specification, pages 34-35, lines 32-33 and 1-2. Again, **this would allow one of skill in the art to better diagnose cancer and other disorders of cell proliferation**. Applicants further note that these methods for determining the proliferative status of cancer cells are carried out by determining the ability of proliferative cells to bind σ_1 and $\sigma_{1\beta}$ ligands, respectively. The ratio of $\sigma_{1\beta}$ to σ_1 density on a cell is an indicator of the proliferative state of the cell. Applicants further note that σ receptors have been defined as nonopiate, nondopaminergic, and nonphencyclidine receptors based on their ligand binding characteristics. *See, e.g.*, Thomas, *Life Sci.* 46:1279-1286 (1990); Bem, et al., *Cancer Res.* 51: 6558-6562 (1991); John, et al., *J. Nucl. Med.* 37:267P (1996); John, et al., *J. Nuc. Med.* 34:2169-2175 (1993); John, et al., *J. Med. Chem.* 37:1737-1739 (1994); John, et al., *Life Sci.* 56:2385-2392 (1995); John, et al., *J. Nucl. Med.* 37:205P (1996). **Thus, the present application allows for one of skill in the art to determine the proliferative status of σ_{1B} and determine a ratio of σ_{1B} activity in tumor regions of interest versus normal tissue.** Accordingly, there is a well established utility for σ_{1B}. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejections to Claims 4-7, 11 and 33.

Applicants further submit that methods for determining the proliferative state of a cell by determining the cell's ability to bind σ_2 receptors may now be carried out using a cell's ability to bind $\sigma_{1\beta}$. These methods are described in international patent applications PCTUS97/04403 (claiming priority from US Provisional Application Number 60/013,717) and PCT/US00/13834 (claiming priority from U.S. Provisional Application No. 60/135,274), and in Wheeler et al., *Br. J. Cancer* **86**, 1223-1234 (2000), all of which are hereby incorporated in their entirety.

Applicants further submit that U.S. Patent No. 6,676,925 illustrates the utility of the present application. It provides a noninvasive method to detect cancer cells or to assess the proliferative status of cancer cells which express sigma-2 receptors, such as cells of solid tumors, in vitro or in vivo. Because the $\sigma_{1\beta}$ receptor exhibits σ_2-like binding it too can be utilized to assess the proliferative status of cancer cells. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections to Claims 4-7, 11 and 33.

IV. Rejections under 35 U.S.C. § 112, first paragraph (enablement)

Claims 1, 4-7, 11 and 33 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention and as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse these rejections due to the amendments to the claims and the reasons enumerated in the response to the 35 U.S.C. § 101 rejections and enumerated below.

Applicants note that the "test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." (MPEP §2164.01, citing *In re Wands*, 858 F.2d 731, 737). Applicants note that Claims 1 and 11 recite specific structurally related sequences which encode for a $\sigma_{1\beta}$ receptor whose functionality and biological activity has been disclosed throughout the specification. The Applicants have provided the nucleotide sequence, SEQ ID NO: 1 and the amino acid sequence, SEQ ID NO: 2. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections to Claims 1, 4-7, 11 and 33.

Furthermore, Applicants submit that the Wands Factors have been met. First, Applicants submit that one of skill in the art could perform the experimentation necessary to achieve what is claimed. Applicants further submit that the claims are directed to specific polynucleotides or methods of producing a protein. The claims do not recite the use of any non-functional variant. Furthermore, Applicants submit that σ_2 activity has been disclosed as discussed above. Second, Applicants submit that the specification provides the proper direction and guidance needed. Applicants additionally submit that the variants determine the proliferative status of a tumor that comprises cells that express $\sigma_{1\beta}$ receptors and as such are well defined, as according to the recitations of Claim 1, they must encode a $\sigma_{1\beta}$ receptor which exhibits σ_2 activity. Applicants submit that one of skill in the art would readily be able to produce the results of the claims of the present application. Accordingly, Applicants

respectfully request reconsideration and withdrawal of the 35 U.S.C. §112, first paragraph rejection to Claims 1, 4-7, 11 and 33.

V. Rejections under 35 U.S.C. § 112, first paragraph (written description)

Claims 1, 4-7, 11 and 33 also stand rejected under 35 U.S.C. § 112, first paragraph as allegedly not containing subject matter described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. Applicants respectfully disagree with this assertion for the reasons enumerated in the previous sections and for the reasons discussed below.

Applicants note that the United States Patent and Trademark Office has provided guidelines regarding the policy objectives of the written description requirement. The guidelines explain that the policy goals are to i) clearly convey to the public what was invented; ii) put in possession of what the applicant claims as the invention; and iii) prevent an applicant from claiming subject matter that was not described in the specification as filed. Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1104-05 (Jan. 5, 2001). Applicants note that the specification discloses that SEQ ID NO:1 is the human mRNA (cDNA) sequence of $\sigma_{1\beta}$, and SEQ ID NO:2 is the human $\sigma_{1\beta}$ amino acid sequence. Therefore, the structure of the invention has been clearly established and one of skill in the art could readily predict the structure as claimed. Applicants additionally note that Claim 1 recites that the polynucleotides comprising SEQ ID NO: 1 or that encode SEQ ID NO: 2 are at least 95% similar to SEQ ID NO: 1 or SEQ ID NO: 2 and encode a $\sigma_{1\beta}$ receptor. Applicants have provided hybridization conditions for such activity in the specification. Applicants further note that it may be advantageous to produce nucleotide sequences encoding $\sigma_{1\beta}$ or its derivatives possessing a substantially different codon usage. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding $\sigma_{1\beta}$ and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence. Applicants further submit that for the

reasons discussed above, there is clear evidence of activity of a $\sigma_{1\beta}$ receptor. Accordingly, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112, first paragraph rejections.

Furthermore, Applicants submit that computer algorithms can readily calculate the possible sequences and their substitutions. Applicants submit that such algorithms are incorporated into the NBLAST AND XBLAST programs of Altschul et al. (*J. Mol. Biol.* 215:403-410 1990). Such programs are readily obtainable and easily used by those of skill in the art. Of course, such polynucleotides would encode a $\sigma_{1\beta}$ receptor exhibiting σ_2 activity which could be readily tested by an assay such as that described in Example 4 of the application.

Additionally, Applicants note that the United States Patent and Trademark Office has clarified the standard for examining applications for compliance with respect to the written description requirement of 35 U.S.C. §112, first paragraph. These guidelines state, in part:

> The examiner has the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed . . .. Consequently, rejection of an original claim for lack of written description should be rare.

66 Fed. Reg. 1099, 1105 (Jan. 5, 2001) (emphasis added). Applicants respectfully contend that the specification does provide a sufficient written description so that one skilled in the art would appreciate that the Applicant was in possession of the claimed invention at the time of filing. Applicants submit that a person of skill in the art can readily envision polynucleotides comprising SEQ ID NO. 1, encoding SEQ ID NO. 2 or active fragments thereof. Accordingly, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 112, first paragraph to Claims 1, 4-7, 11 and 33.

V. 35 U.S.C. § 102, anticipation rejections

Claim 33 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Malliga et al. Applicants respectfully traverse this rejection as set forth below.

Section 102(b) of Title 35 of the United States Code bars the issuance of a patent if "the invention was patented ... more than one year prior to the date of the application for

patent in the United States." "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631 (Fed.Cir.1987). Additionally, anticipation under 35 U.S.C. § 102 requires the disclosure in a single piece of prior art of each and every limitation of a claimed invention. *Apple Computer Inc. v. Articulate Systems Inc.* 57 USPQ2d 1057, 1061 (Fed. Cir. 2000). "It is well settled that a prior art reference may anticipate when the claim limitations not expressly found in that reference are nonetheless inherent in it. Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates." *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed.Cir.2002) (citations and internal quotation marks omitted). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." In re Robertson, 169 F.3d 743, 745 (Fed.Cir.1999) (citations and internal quotation marks omitted).

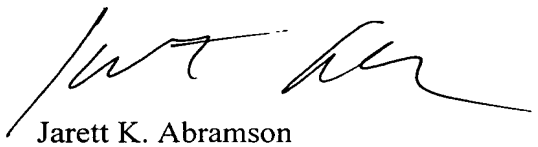
Applicants submit that Malliga et al. does not anticipate nor render inherent the present invention. Applicants submit that the Office Action note that the cells of Milliga et al. are not transformed with the polynucleotide of Claims 1. Thus, Applicants submit that Malliga et al. fails to disclose the peptides of Claim 1. Therefore, **the transformed cell comprising the polynucleotide of Claim 1 could not be disclosed by Malliga et al**. Applicants submit that because Claim 33 depends from Claim 1, and Claim 1 is novel as each and every element of the invention is not disclosed, therefore, Claim 33 is novel. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection to Claim 33.

CONCLUSION

In view of the remarks presented herein, Applicants respectfully submit that the claims define patentable subject matter. If, in the opinion of the Examiner, a telephonic conference would expedite the examination of this matter, the Examiner is invited to call the undersigned attorney, Jarett K. Abramson, at (919) 854-1400.

It is not believed that an extension of time and/or additional fee(s)-including fees for net addition of claims-are required, beyond those that may otherwise be provided for in documents accompanying this paper. In the event, however, that an extension of time is necessary to allow consideration of this paper, such an extension is hereby petitioned under 37 C.F.R. §1.136(a). Any additional fees believed to be due in connection with this paper may be charged to our Deposit Account No. 50-0220.

Respectfully Submitted,



Jarett K. Abramson
Registration No. 47,376

USPTO Customer No.: 20792
Myers Bigel Sibley & Sajovec, P.A.
Post Office Box 37428
Raleigh, NC 27627
Telephone (919) 854-1400

CERTIFICATE OF EXPRESS MAILING

Express Mail Label No. EV675782996US
Date of Deposit: April 29, 2005

I hereby certify that this correspondence is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR § 1.10 on the date indicated above and is addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Katie A. Chung